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OFFICE OF
SOLID WASTE AND EMERGENCY
RESPONSE

June 12, 2003

OSWER No. 9285.7-75

Marcia L. Bailey, D. Env.
Environmental Toxicologist
U.S. Environmental Protection Agency, Region 10
Office of Environmental Assessment, Risk Evaluation Unit
1200 Sixth Avenue, OEA-095
Seattle, Washington 98101

Dear Dr. Bailey:

I am responding to recent inquiries concerning cancer toxicity values to evaluate inhalation and ingestion risks from exposure to tetrachloroethylene, also commonly known as perchloroethylene or "PCE," and specifically whether it would be appropriate to use a California Environmental Protection Agency (Cal EPA) inhalation unit risk value and oral slope factor. This letter supercedes an earlier version of this letter, which identified an incorrect source of the oral slope factor. This letter is consistent with the earlier letter regarding the inhalation unit risk value and its source.

In the absence of relevant values in the U.S. Environmental Protection Agency (EPA) Integrated Risk Information System (IRIS) or a value from EPA's National Center for Environmental Assessment/Superfund Technical Health Risk Support Center (STSC), which are the first two tiers of human health toxicity values in the EPA Superfund hierarchy, we would support consideration of the Cal EPA inhalation unit risk value from the Air Toxics Hot Spots Program and the oral slope factor from the Cal EPA Public Health Goal in Drinking Water.

In general, Cal EPA develops its toxicity values in a manner which is quite similar to the EPA IRIS program, in that many of the same databases and considerations are used. Cal EPA's assessments used information from some of the same sources or studies that EPA typically considers in the IRIS program, including the most recent relevant studies known to exist, and also considered this information in a manner similar to the EPA IRIS program.

In summary, having consulted on this matter with the STSC, the Office of Emergency and Remedial Response (OERR) supports use of the Cal EPA Air Toxics Hot Spots Program inhalation unit risk of $5.9 \text{ E-6 } (\mu\text{g}/\text{m}^3)^{-1}$ for Superfund sites as the best value available at this time until a U.S. EPA value becomes available. Having consulted with the STSC about the Cal EPA Public Health Goal in Drinking Water oral slope factor of $5.4\text{E-1 } (\text{mg}/\text{kg-day})^{-1}$ for PCE, we also support the use of this value until a U.S. EPA value becomes available.

The Cal EPA presents a full, complete and transparent presentation of the relevant information on their development of these values on their internet website. Documentation on the Air Toxics Hot Spots Program inhalation unit risk value can be found at this internet website: http://www.oehha.ca.gov/air/hot_spots/pdf/TSDNov2002.pdf . Since this website does not take you directly to the PCE discussion, and this can be difficult to find on the internet website, we have downloaded the eight pages pertaining to PCE and include them as an enclosure to this letter. Documentation on the Public Health Goal in Drinking Water oral slope factor can be found at this Cal EPA internet website: <http://www.oehha.ca.gov/water/phg/pdf/PCEAug2001.pdf> . Because of the size of this document (75 pages) and because this website does take you directly to this document, we have not included this document as an enclosure to this letter. With respect to the transparency of any Superfund Program decisions which may use these values in selecting a response action, we recommend that the appropriate documentation from the Cal EPA website be provided, or the link to the relevant Cal EPA internet website be identified.

Thank you for your inquiry. If you have any questions, please contact Mr. Dave Crawford of my staff at (703) 603-8891.

Sincerely,

/s/

Elizabeth Southerland, Deputy Director
Office of Emergency and Remedial Response

cc: Harlal Choudhury ORD/NCEA/STSC
Sarah Levinson, Region 1
Matthew Hale, OSWER/OSW
Barnes Johnson, OSWER/OSW
Renee Wynn, OSWER/FFRO
James Woolford, OSWER/FFRO
Regional Risk Leads, Regions 1-10
Nancy Riveland, Superfund Lead Region Coordinator, USEPA Region 9
Paul Sieminski, RCRA Lead Region Coordinator, USEPA Region 6
OERR NARPM Co-Chairs
Joanna Gibson, OERR Document Coordinator

Enclosure: California Environmental Protection Agency, Office of Environmental Health Hazard Assessment, Air Toxics Hot Spots Program Risk Assessment Guidelines, Part II, Technical Support Document for Describing Available Cancer Potency Factors, December 2002 (excerpt pertaining to tetrachloroethylene)

PERCHLOROETHYLENE¹

CAS No: 127-18-4

I. PHYSICAL AND CHEMICAL PROPERTIES (From HSDB, 1998)

Molecular weight 165.83

Boiling point 121°C

Melting point -19 °C

Vapor pressure 18.47 mm Hg @ 25°C

Air concentration conversion 1 ppm = 6.78 mg/m³ @ 25°C

II. HEALTH ASSESSMENT VALUES

Unit Risk Factor: 5.9 E-6 (µg/m³)-¹

Slope Factor: 2.1 E-2 (mg/kg-day)-¹

[Male mouse hepatocellular adenoma and carcinoma incidence data (NTP, 1986), cancer risk estimate calculated using a linearized multistage procedure and PBPK model dose adjustment (CDHS, 1991).

III. CARCINOGENIC EFFECTS

Human Studies

Epidemiological studies of perchloroethylene (PCE) exposure have been reviewed by Reichert (1983) and by the U.S. EPA (1985). Blair *et al.* (1979) analyzed the death certificates of 330 union laundry and dry-cleaning workers (out of a cohort of 10,000). Of 330 decedents, 279 had worked solely in dry-cleaning establishments. Increased mortality from cancers of the respiratory tract, cervix, and skin was documented, and when all malignancies were evaluated together, the number of observed deaths was significantly greater than expected ($p < 0.05$). Although an excess of liver cancer and leukemia was also observed, these increases were not statistically significant.

In an expanded study, Blair *et al.* (1990) reported on mortality among 5,365 dry cleaning union members. Statistically significant excesses of cancer of the esophagus and cervix and non-significant excesses for cancer of the larynx, lung, bladder, and thyroid were reported. Lack of PCE exposure data and lack of accounting for potential confounding factors, such as economic

¹This document was copied from the California Environmental Protection Agency/Office of Environmental Health Hazard Assessment (OEHHA) website (<http://www.oehha.ca.gov/risk/chemicalDB/index.asp>) by the U.S. Environmental Protection Agency/Office of Emergency and Remedial Response on March 18, 2003. Formatting required that the pages be renumbered and that Table 1 be retyped into this document, as it had originally been presented on the OEHHA website.

status, tobacco, or alcohol use, prevents any firm conclusion as to the association of PCE exposure and excess cancer.

Katz and Jowett (1981) analyzed the mortality patterns of 671 white female laundry and dry-cleaning workers. Occupational codes listed on the certificates did not distinguish between the two types of work. Data on the duration of employment were not available, nor were the investigators able to determine to which solvent(s) the individuals were exposed. Smoking history was not known. A significant increase in risk of death from cancer of the kidneys ($p < 0.05$) and genitals ($p < 0.01$) was 480 documented. An excess risk from skin and bladder cancer was also found; however, neither increase was statistically significant.

Other studies of laundry and dry-cleaning workers have also reported an increased risk of death from cervical cancer (Blair *et al.*, 1979; Kaplan, 1980); however, these investigators have not compared mortality data by low-wage occupation. Although not definitive, the findings of Katz and Jowett (1981) suggest that factor(s) other than (or in addition to) solvent exposure are important contributors to cervical cancer.

Kaplan (1980) completed a retrospective mortality study of 1,597 dry-cleaning workers exposed to PCE for at least one year (prior to 1960). The solvent history of approximately half of the dry-cleaning establishments was known. The inability of Kaplan to quantify solvent exposure adds an important confounding variable to the study (Kaplan, 1980). The mean exposure concentration of individuals to PCE was calculated to be 22 ppm for dry-cleaning machine operators and 3.3 ppm for all other jobs. Kaplan found an elevated SMR (182) for malignant neoplasms of the colon (11 observed deaths, 6.77 to 6.98 expected deaths). In addition to colon cancer, malignant neoplasms of the rectum, pancreas, respiratory system, urinary organs, and "other and unspecified sites (major)" were observed (Kaplan, 1980). Although the relatively small cohort in this study limits conclusions about the carcinogenic potential of PCE, the study (Kaplan, 1980) results suggest a relationship between colon cancer and solvent exposure.

A group of Danish laundry and dry-cleaning workers was identified from the Danish Occupational Cancer Register (Lyng *et al.*, 1990). From cancer incidence data for a 10-year period, a significant excess risk was found for primary liver cancer among 8,567 women (standardized incidence ratio 3.4, 95% confidence interval 1.4-7.0). No case of primary liver cancer was observed among 2,033 men, for whom the expected value was 1.1. Excess alcohol consumption did not appear to account for the excess primary liver cancer risk for women. However, no data was available on actual exposures of the study group to PCE or other chemicals.

Duh and Asal (1984) studied the cause(s) of mortality among 440 laundry and dry-cleaning workers from Oklahoma who died during 1975 to 1981. Smoking histories were not available and separation of the two groups by occupation was not possible. NIOSH reported that, although 75% of dry-cleaning establishments in the U.S. use PCE, Oklahoma may be unique in that petroleum solvents account for more than 50% of total solvents used during this period (NIOSH,

1980). Analysis of deaths due to cancer showed an increase for cancers of the respiratory system, lung, and kidney.

Brown and Kaplan (1987) conducted a retrospective, cohort-mortality study of workers employed in the dry-cleaning industry to evaluate the carcinogenic potential from occupational exposure to PCE. The study cohort consisted of 1,690 members of four labor unions (located in Oakland, Detroit, Chicago, and New York City). Individuals selected for the study had been employed for at least one year prior to 1960 in dry-cleaning shops using PCE as the primary solvent. Complete solvent-use histories were not known for about half of the shops included in the study. Because petroleum solvents were widely used by dry cleaners prior to 1960, most of the cohort had known or potential exposure to 481 solvents other than PCE (primary, various types of Stoddard solvents). The investigators also identified a subcohort of 615 workers who had been employed only in establishments where PCE was the primary solvent. The PCE exposure in shops included in the study was evaluated independently (Ludwig *et al.*, 1983). The geometric mean of time-weighted-average exposures was 22 ppm PCE for machine operators and approximately 3 ppm for other workers.

In summary, a statistically significant excess of deaths from urinary tract cancer was observed in those workers that were potentially exposed to both PCE and petroleum solvents. Individuals employed in shops where PCE was the primary solvent did not have an increased risk of mortality from kidney or bladder cancer. Although these findings do not rule out PCE as the causative agent of urinary tract cancer, the data suggest that other factors or agents may have contributed to the development of neoplastic disease. CDHS stated in the Toxic Air Contaminant document "Health Effects of Tetrachloroethylene" that until studies are completed that include a thorough analysis and quantification of PCE exposures, epidemiological studies will not be useful for the assessment of the human health risks of PCE (CDHS, 1991).

Animal Studies

Two lifetime bioassays have been completed on PCE (NCI, 1977; NTP, 1986). Additionally, three other studies have addressed the question of PCE carcinogenicity (Rampy *et al.*, 1978; Theiss *et al.*, 1977).

The National Cancer Institute (NCI) conducted a study in which B6C3F₁ mice and Osborne Mendel rats were administered PCE in corn oil by gavage, 5 days/week for 78 weeks (NCI, 1977). The timeweighted average daily doses of PCE were 536 and 1072 mg/kg for male mice, 386 and 722 mg/kg for female mice, 471 and 941 mg/kg for male rats, and 474 and 949 mg/kg for female rats. PCE caused a statistically significant increase in the incidence of hepatocellular carcinomas in mice of both sexes and both dosage groups ($p < 0.001$). The time to tumor development was considerably shorter in treated than in control mice. In untreated and vehicle control mice, hepatocellular carcinoma were first detected at about 90 weeks. In comparison, hepatocellular carcinomas in male mice were detected after 27 weeks (low dose) and 40 weeks (high dose) and in female mice after 41 weeks (low dose) and 50 weeks (high dose) (Table 1). The median survival times of mice were inversely related to dose. For control, low dose and high dose male

mice, their median survival times were 90 weeks, 78 weeks and 43 weeks, respectively; for female mice, their median survival times were 90 weeks, 62 and 50 weeks, respectively. Early mortality occurred in all groups of rats dosed with PCE. NCI (1977) determined that the early mortality observed in rats in this bioassay were inappropriately high and because the optimum dosage was not used, the rat results preclude any conclusions regarding the carcinogenicity of PCE in rats. In addition, the PCE used in the NCI mouse and rat bioassays had a purity of 99%, with epichlorohydrin (ECH) used as a stabilizer. It has been suggested that the presence of this contaminant may have directly contributed to tumor induction.

The most definitive study of the carcinogenic potential of PCE was conducted by Battelle Pacific Northwest Laboratories for the National Toxicology Program (NTP, 1986). In this experiment, 482 B6C3F₁ mice and F344/N rats were exposed to 99.9% pure PCE by inhalation, 6 hours/day, 5 days/week for 103 weeks. Mice were exposed to concentrations of 0, 100, or 200 ppm; rats were exposed to concentrations of 0, 200, or 400 ppm. Both exposure concentrations produced significant increases in mononuclear cell leukemia in female rats (incidence in control, 18/50 animals; in rats receiving 200 ppm, 30/50; and in rats receiving 400 ppm, 29/50). Treated male rats also developed mononuclear cell leukemia in greater numbers than controls (controls, 28/50 animals; 200 ppm, 37/50; 400 ppm, 37/50) [Table 1]. Male rats (at the 200 ppm and 400 ppm PCE exposure levels) exhibited an increased incidence of both renal tubular-cell adenomas and adenocarcinomas. Although the increases were not statistically significant, they appeared to be dose-related.

Brain glioma (a rare tumor of neuroglial cells) was observed in one male control rat and in four male rats that were exposed to 400 ppm PCE (NTP, 1986). This increase was not statistically significant. However, because the historical incidence of these tumors is quite low (0.2% at Battelle Laboratories), the increased incidence in treated animals in this study is noteworthy. Both concentrations of PCE produced a statistically significant increase of hepatocellular carcinomas in treated mice of both sexes ($p < 0.001$). The incidence of these carcinomas in male mice was as follows: controls, 7/49 animals; low-dose, 25/49; and high-dose, 26/50. The incidence of hepatocellular carcinomas in treated female mice was: controls, 1/48 animals; low-dose, 13/50; high-dose, 36/50. Hepatocellular adenomas occurred in both sexes of mice and at both concentrations of PCE (Table 1). The incidence of adenomas was not statistically significant. However, the combined incidence of hepatocellular adenomas and hepatocellular carcinomas was significant. In males, the combined incidence was: controls, 16/49 animals; low-dose 31/49; ($p = 0.002$); adenomas and carcinomas was: controls, 4/48 animals; low-dose, 17/50 ($p = 0.001$); and high-dose, 38/50 ($p < 0.001$).

Table 1: PCE-induced tumor incidence in mice and rats

Study	Species	Sex	Concentration or dose	Tumor response	
				Type ^a	Incidence
NCI, 1977	Mice	Males	0 mg/kg-d	HC	2/17
			536 mg/kg-d	HC	32/49*
			1072 mg/kg-d	HC	27/48*
		Females	0 mg/kg-d	HC	2/20
			386 mg/kg-d	HC	19/48*
			772 mg/kg-d	HC	19/48*
NTP, 1986	Mice	Males	0 ppm	HC; HAC	7/49; 16/49
			100 ppm	HC; HAC	25/49*; 8/49 (NS)
			200 ppm	HC; HAC	26/50*; 18/50 (NS)
		Females	0 ppm	HC; HAC	1/48; 3/48
			100 ppm	HC; HAC	13/50*; 6/50 (NS)
			200 ppm	HC; HAC	36/50*; 2/50 (NS)

^a HC=hepatocellular carcinomas; HAC=hepatocellular adenoma; ML=mononuclear cell leukemia

*p< 0.001, Fisher Exact Test; **Probability Level, Life Table Analysis, NS= not statistically significant

The NTP (1986) determined that, under the conditions of the study, there was “clear evidence of carcinogenicity” of PCE for male F344/N rats, “some evidence of carcinogenicity” of PCE for female 483 F344/N rats, and “clear evidence of carcinogenicity” of PCE for both sexes of B6C3F₁ mice. IARC reevaluated the evidence of carcinogenicity of PCE in 1987 using data from the NTP study and concluded that there was sufficient evidence that PCE is carcinogenic to animals (IARC, 1987). Other studies on PCE included those by Rampy *et al.* (1978) and Theiss *et al.* (1977). Rampy *et al.* (1978) exposed male and female Sprague-Dawley rats to PCE by inhalation (300 or 600 ppm) 6 hours/day, 5 days/week for 12 months. Animals were subsequently observed for 18 months. Pathological changes in the liver or kidney were not observed. Theiss and coworkers studied the ability of PCE to induce lung adenomas in A/St male mice (Theiss *et al.*, 1977). Animals 6 to 8 weeks old were given 80, 200, or 400 mg/kg of PCE in tricapylin (intraperitoneally) three times a week. Each group received 14, 24, or 48 injections. Treated animals did not exhibit a significant increase in the average number of lung tumors when compared to controls.

IV. DERIVATION OF CANCER POTENCY

Basis for Cancer Potency

Perchloroethylene has been observed to induce mononuclear cell leukemia in male and female rats and liver tumors in male and female mice (NTP, 1986). CDHS (1992) decided that the tumor incidence data from this study were suitable for use in developing a quantitative risk assessment.

Methodology

Results from the 1986 NTP inhalation study were used as the basis for estimating the carcinogenic risk of PCE to humans. In this bioassay, PCE was 99.9% pure, and animals were exposed 6 hours/day, 5 days/week for 103 weeks. The mice in the 100 and 200 ppm dose groups were exposed to a timeweighted- average (TWA) of 16 and 32 ppm, respectively (e.g., 100 ppm \times 6 hours/24 hours \times 5 days/7 days). Similarly, rats in the 200 and 400 ppm dose groups were exposed to a TWA of 33 and 66 ppm, respectively.

The CDHS staff used the metabolized dose, adjusted to continuous lifetime exposure, to calculate the carcinogenic potency of PCE (CDHS, 1992). There are several uncertainties using this approach: 1) It was assumed that oxidative metabolism leads to the production of carcinogenic metabolites but the ultimate carcinogen(s) has not been well characterized. The metabolism of PCE is not well quantified in humans, and 20-40% of the absorbed PCE has not been accounted for. 2) The pharmacokinetic models used do not account for individual differences in metabolism and storage. The body burden depended on factors such as age, sex, exercise or workload, body mass, adipose tissue mass, pulmonary dysfunctional states, and individual differences in the intrinsic capacity to metabolize PCE. Two pharmacokinetic models, the steady-state and the PB-PK approaches were used. They incorporated an 18.5% estimated applied dose as the fraction of the dose that is metabolized in humans. For the low-dose PCE risk assessment, the Crump multistage polynomial (Crump, 1984) was chosen.

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This model, rather than a time dependent form of the multistage model, was chosen because most tumors were discovered only at the time of sacrifice, and survival in this study was relatively good. The cancer potency values derived using the two different pharmacokinetic approaches using the 1986 NTP rat and mouse studies ranged from 0.12 - 0.95 (mg/kg-d)⁻¹. When expressed as a function of human applied dose the values obtained ranged from 0.0025 to 0.093 (mg/kg-d)⁻¹. Using an estimated human weight of 70 kg, estimated breathing rate of 20 m³/day and the PCE conversion factor of 1 ppb = 6.78 μ g/m³, the cancer unit risk values for PCE ranged from 0.2 - 7.2 \times 10⁻⁵ (ppb)⁻¹. After considering the quality of the cancer bioassays and the uncertainty of human metabolism, CDHS (1992) decided that the best value for the PCE cancer unit risk was 4.0 \times 10⁻⁵ (ppb)⁻¹ [5.9 \times 10⁻⁶ (μ g/m³)⁻¹]. This value is derived from the tumor incidence data for the most sensitive species, sex, and tumor site, male mouse hepatocellular adenomas or carcinomas (NTP, 1986).

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